Environmental Health Perspectives
Vol. 20, pp. 27–37, 1977

Environment and the Skin

by Raymond R. Suskind*

The skin is an important interface between man and his environment; it is an important portal of entry for hazardous agents and a vulnerable target tissue as well. It is a uniquely accessible model system for detecting hazards and for studying mechanisms of a wide variety of biologic functions.

Environmental causes of skin reactions comprise a vast array of physical, chemical and biological agents. To appreciate the role of the skin as an interface with man's environment, it is necessary to understand the multiple adaptive mechanisms, and the defenses of the skin against the environmental stresses. The skin is endowed with a versatile group of defenses against penetration, fluid loss from the body, thermal stress, solar radiation, physical trauma and microbial agents. Patterns of adverse response range in quality and intensity from uncomplicated itching to metastatic neoplasia. Environmental problems comprise a large segment of disabling skin disease. Although critical epidemiologic data is limited, cutaneous illnesses comprise a significant segment of occupational disease. This represents a significant loss in productivity and a major cause of disability.

The most serious research needs include the development of surveillance systems for identifying skin hazards and determining frequency of environmental skin disease; the development of new models for studying cutaneous penetration; the elucidation of the mechanisms of nonallergic inflammatory reactions (primary irritation) and of the accommodation phenomenon; the development of more sensitive models for predicting adverse responses to marginal irritants; the utilization of modern skills of immunobiology and immunochemistry to elucidate mechanisms of allergic responses; the launching of epidemiologic studies to determine the long term effects of PCBs and associated compounds such as dioxins; and the expansion of research in the mechanisms of skin cancer in relation to susceptibility, genetic and metabolic considerations, ultraviolet light, and phototoxic agents.

Environmental Skin Disease: Scope and Size of the Problem

It is somewhat obvious that the skin with its large surface in direct contact with the environment, natural as well as man-made, is among the most vulnerable of organ systems. It is not surprising to find that skin diseases of environmental origin including chemical stimuli, physical stresses, and infectious agents collectively comprise the majority of skin illness, and this is numerically a most important segment of disabling acute and chronic skin disease. If, as a clue to the relative importance of environmental factors, one just considers that segment of skin diseases provoked by occupational environments alone (as in industry and agriculture which only includes compensable cases) the statistics are quite convincing. The incidence of occupational skin diseases, as gleaned from workmen's compensation statistics, has in the past years ranged from 25 to 80% of all occupational diseases (*1*). This represents an enormous loss of productivity each year and a major cause of disability (*1*).

In considering man's concern about the quality of his environment and the hazards to health which may be present in air, water, occupational settings, transportation uses, consumer products including foods, fabrics, and household materials, it is appropriate to question what part the skin plays in this dilemma.

The skin is an important interface between man and his physical, chemical and biologic environment. It is an important portal of entry of potentially hazardous agents; it is a vulnerable target tissue for damage by environmental agents. It is a uniquely accessible model system for detecting hazards and for studying mechanisms of a wide variety of biologic functions, including adaptive processes and adverse reactions.

Properly to appreciate the role of the skin as an important interface with man's environments, it is necessary to understand the multiple adaptive mechanisms and the defenses which the skin provides against environmental stresses. It is useful to

*Institute of Environmental Health, University of Cincinnati Medical Center, Cincinnati, Ohio 45267.

recognize the variation in such mechanisms and the adverse responses which are influenced by genetic considerations, age, cultural factors including working conditions, social institutions, technological factors, etc. It is essential to understand the physiological and biochemical aspects of percutaneous absorption and the factors which enhance cutaneous penetration; the pathologic patterns of response to environmental injury and the agents which are known to induce them; as well as the preventive approaches to cutaneous hazard. Specific patterns of adverse response can be characterized by morphologic, physiologic and biochemical features. Such reactions range in quality and intensity from uncomplicated itching to metastatic neoplasia.

Cutaneous Defenses and Adaptation

The skin is a primary organ of defense and homeostasis (*2, 3*). It is endowed with a versatile group of defenses against penetration by chemical agents, fluid loss from the body, thermal stress, solar radiation, physical trauma, and against microbial agents (*2*). These defenses can be characterized on the basis of morphologic features, physiological and biochemical processes (*4, 5*).

One of the most important functional defenses is the epidermal barrier. When intact, it provides a significant defense against penetration by chemical agents and against body water loss. The intact skin acts as a physical barrier to invasion by microorganisms and provides some chemical bacteriostatic protection. The intact skin is infected with great difficulty.

The skin offers limited protection against acidic and alkaline substances by virtue of the buffering action of surface components, e.g., amphoteric amino acids, lactic acid, and lactate which are deposited in the stratum corneum by eccrine sweat and from epidermal debris. The diffusion of CO_2 from within the skin to the surface may also play a role in the neutralization process. Eccrine sweat may act as a diluent and decrease the effect of a water soluble noxious agent. On the other hand, it may promote hydration and maceration of the barrier and promote absorption. The free fatty acids derived from enzymatic action on sebaceous triglycerides have antimicrobial action. The odd-numbered C_5, C_7, C_9, C_{11}, and C_{13} are more potent fungistatic agents than the even-numbered neighbors. The long-chain unsaturated acids are bacteriostatic for a limited group of organisms and to some degree provide a self-disinfecting mechanism.

The epidermal and pigment components provide defenses against ultraviolet radiation injury. The pigment of the skin is synthesized in the melanin-producing cells, the melanocytes, from which it is conveyed in granular form to adjacent cells of the basal layer, the prickle cells, and is finally desquamated with the horny shingles at the surface. Normal skin pigment serves as a protection against damage by actinic radiation. Under suitable stimulus of ultraviolet radiation, the rate of pigment formation increases and already existing pigment darkens. The pigmentary response to ultraviolet light, as well as corneal thickening, provides for added protection against further actinic radiation injury. Within recent years, new and revealing information has been developed about the complex biochemical synthesis of melanin. It has provided for a much better understanding of pigment disturbances in the skin and especially those provoked by occupational exposures. The starting point of the synthesis of melanin is the tyrosine, which, in the presence of the copper-protein complex tyrosinase and oxygen, is transformed into dihydroxyphenylalanine, or dopa. This initial product, in turn, acts as an additional catalyst to increase the rate of transformation of the precursor tyrosine, into dopa. From dopa to the final product melanin there are a series of intermediate steps in which substances such as dopaquinone, dopachrome, 5,6-dihydroxyindole, and indole-5,6-quinone are sequentially evolved before polymerization to the melanins occur. A variety of physiologic factors regulate the formation of melanin, and particular environmental stimuli will alter pigmentation in the skin. Some of the most dramatic pigment changes are produced as a consequence of occupational and other environmental exposures. The mechanism of some of these changes are discussed below.

Dermal resiliency provides a measure of resistance against traumatic injury. The corium or dermis which lies beneath the epidermal cover is made chiefly of connective tissue cells and fibers as well as a matrix of ground substance all of which have important functions. The tough fibrous components provide a resilient barrier against trauma as well as a supporting structure for the blood vessels, nerves, and the skin appendages; the cellular elements of mesenchymal origin play an important role both in the development and maintenance of the fibrous structure as well as providing a second line of defense against injury by physical stimuli, chemical agents and infecting microorganisms. The cells are involved in wound healing and repair after the damage is done. The role of the ground substance may be greater than we presently believe. It does act as a means of transferring nutrients and metabolites to and from the structures within its surroundings.

The action of small vessels in the dermis and

sweat glands provides the essential homeostatic mechanism for human thermal regulation. The vascular bed of the skin, by virtue of continuous alteration in rate of blood flow, plays a critical role in thermal regulation at environmental temperatures of 25 to 31°C (zone of vascular control). The thermal regulation function of the eccrine sweat gland is accomplished by the surface evaporation of water at critical temperatures. Active sweating occurs after the small vessels have reached maximum dilatation and maximum heat loss by radiation. Both of these are important homeostatic mechanisms.

The immunobiologic processes in which both B and T cells are involved respond defensively to infectious agents and react to chemical stimuli. These include recognition mechanisms which involve either humoral antibodies or cell-mediated hypersensitivity responses. The latter are observed in allergic contact dermatitis and delayed hypersensitivity reactions to inhaled or ingested agents.

The neural components of the skin, through a variety of sensory mechanisms, provide the individual with information about the state of the external environment. We appreciate touch, temperature, pressure, and pain. It is via the sensory elements of the skin that an individual is constantly in touch with noxious elements in the environment.

Percutaneous Absorption

Understanding the significance of skin penetration requires a knowledge of the structural and biochemical aspects of the epidermal barrier; a recognition of the potential portals as well as their behavior when the skin is exposed to chemical penetrants, including modes and routes of transfer, and, of course, the important factors which influence rate of transfer (*6–11*).

The epidermal barrier to the passage of water and other chemical penetrants is the stratum corneum. This is composed of bonded and interdigitating keratinized cells. It is a compact structure except for the outermost layers which are being shed continuously. It can hardly be regarded as a uniform membrane, but it is a composite made up of at least 10 distinct cell layers which means 20 distinct cellular membranes. Membranes of those keratinized cells are different from those of the Malpighian layer. Rather than the usual 80 Å unit membrane, the corneum cell membrane has a modified membrane of about 200 Å in thickness. It is likely that this thickened version of the cell membrane contributes significantly to the barrier properties of the stratum corneum. The penetration process appears to be that of passive diffusion. An important factor is the ratio of solubility of the penetrant in the vehicle or solvent to its solubility in the stratum corneum. The partition coefficient is directly proportional to the permeability constant. Factors influencing penetration rate are concentration, temperature, and humidity. The thickness of the horny layer and the time of exposure to the penetrant are also significant factors influencing flux or penetration rate.

There are two major routes of penetration: through the epidermal barrier itself and through the transfollicular or pilosebaceous route. There is little evidence that penetration through the sweat duct occurs with any frequency. There is good evidence, however, that during transient state diffusion, absorption of many substances occurs predominantly through the shunts or the follicles and that steady state diffusion occurs primarily through the intact stratum corneum. Shunt diffusion appears to be dominant in the initial stage of penetration and the transepidermal penetration accounts for a bulk diffusion during the steady state transfer.

Penetration through the skin is enhanced by: physical damage to the stratum corneum, such as abrasion, chemical alteration of barrier components; hydration of the stratum corneum by wetting or high ambient humidity; low-partition coefficient or a low ratio of solubility in the vehicle as compared with the stratum corneum; increasing the duration of exposure and size of skin area involved; increasing temperature (by increasing flux); altering pH, and altering electrical properties of the skin and/or the portals of penetration.

Environmental Factors Which Cause Adverse Skin Reactions

Adverse cutaneous reactions to environmental stimuli represent a wide range of disease problems and encompass a variety of pathological responses to physical, chemical and biological agents.

Physical stresses include friction, pressure, vibration, electricity, high and low ambient temperature, humidity, ultraviolet light, visible light, infrared radiation, and various modalities of ionizing radiation.

Chemical stresses include polar and nonpolar substances, inorganic and organic compounds of a wide range of molecular size, structure, and physical properties. They include water, inorganic acids, alkalis, salts of heavy metals, aliphatic acids, aldehydes, alcohols, esters, hydrocarbons, solvents, metalloorganic compounds, lipids, aromatic and polycyclic compounds, resin monomers and proteins. The chemical agents which are potential irritants or allergic sensitizers predominate. Functionally they include the ubiquitous marginal irritants,

strong irritants, corrosives, and chemical agents which induce delayed and immediate hypersensitivity. There are indeed other important patterns of response which are provoked by agents with specific chemical configuration. In such patterns, a specific anatomical or biochemical component of the skin or its appendages is predominantly involved. These include neoplasia, sebaceous, hair and nail changes, and alteration in pigmentation.

Biological stresses include botanical irritants, sensitizers, phototoxic or photosensitizing plants, viruses, bacteria, fungi, protozoa, and arthropods.

Pathologic Patterns and Reaction Sites

Since the skin is a complex organ system and is histologically heterogeneous, a specific environmental agent may either predominantly affect a single tissue component such as the epidermis or several components, e.g., epidermis, dermis, blood vessels, pilosebaceous unit, melanocytes, etc. (*12*). The type of pathologic pattern may vary with the particular stimulus. Repeated friction may provoke epidermal proliferation and induce thickening of the stratum corneum while an irritant chemical may provoke a mild or severe inflammatory response involving all of the tissues. The predominant features of chronic irritation are epidermal proliferation and thickened stratum corneum, which is a protective response, as well as mild to moderate dermal inflammation.

Identifiable pathologic patterns of reaction to environmental stimuli are given below.

Inflammatory Reactions

The most common pathological response as with most tissues is that of inflammation (*13–22*). It is the characteristic response to a primary irritant and to antigen-induced cell-mediated hypersensitivity reactions. Phototoxic responses, reactions to infections due to microorganisms and due to thermal or mechanical injury, are largely characterized by inflammation. The gross and microscopic features may vary, depending upon the biological characteristics of the hazard and the intensity of the response (*23*). Included in this group are responses to corrosive agents as well as granuloma inducing agents. The most common environmental agents causing such reactions are marginal irritants and contact sensitizers (*17*).

Allergic Reactions

Cutaneous reactions of allergic origin are essentially of two general types. The first of these are reactions induced by antigenic stimuli in which B cells are involved, humoral antibodies developed, and histamine released in the skin in the challenge stage when the host is re-exposed to the antigen. The environmental antigens in such instances usually enter via the respiratory or gastrointestinal tract but rarely percutaneously. Common antigens are drugs such as antibiotics, serum proteins, animal dander, pollens, foods, carbohydrates in bacteria, lipoproteins, agricultural products such as grain dust, wheat flour, etc. The skin test by which hypersensitivity state can be determined is characterized by the immediate wheal and flare response from intradermal or scratch test to the antigen.

The second is cell-mediated hypersensitivity. The allergic contact dermatitis is the most common form of cell-mediated hypersensitivity in the skin. Simple chemical compounds such as nickel or chromium salts, *p*-phenylenediamine, poison ivy resin, etc., are initially absorbed through the skin and conjugate with protein. With notable assistance from macrophages and T cells, the haptene–protein conjugate induces a hypersensitivity state in which re-exposure will provoke an inflammatory response of the eczematous type, such as is commonly seen in poison ivy reactions. Allergic eczematous responses are characterized by erythema, swelling and vesiculation, and usually require several hours (12 to 48 hr) to evoke after a sensitized host is re-exposed. The epicutaneous or patch test is used to identify contact allergic states.

Several test systems can be used to assess hazards of allergenicity. One of the most effective is the human maximization procedure of Kligman (*22*), which possesses both sensitivity and specificity. The other useful tests are the guinea pig maximization test of Magnusson and Kligman (*20*) several modifications of the Landsteiner-Draize test (*24*) using guinea pigs, the repeated insult test in humans, and the open epicutaneous test of Frey et al. (*14, 15*).

The induction of allergic contact dermatitis may involve exposure to ultraviolet light as well. Examples of photoallergens are tetrachlorosalicylanilide, tribromosalicylanilide, bithionol, and phenothiazine and its derivatives.

Benign Epidermal Reactions

Some reactions to environmental agents may be limited largely to the epidermis. This is true for pathological responses to repeated trauma, to filterable viruses such as wart virus, and to physical or chemical agents which induce hyperkeratoses or parakeratoses and calluses.

Pilosebaceous Reactions

Chemical substances of related structure appear to single out the pilosebaceous unit and may alter structure and function specifically (*25–30*). Occupational acne (*12, 25–27*) is a rather common skin disease which may result from exposure to petroleum cutting oils, coal tar fractions, and chlorinated hydrocarbons, such as chlorinated naphthalenes, diphenyls, diphenyl oxides, and chlorinated dioxins. The chlorinated biphenyls are responsible for inducing chloracne and hyperpigmentation (*27*) of the skin as well as hepatic and neurological damage. The chemical stimulus provokes the proliferation of follicular epithelium in the sebaceous duct and follicle opening (infundibulum). These cells become keratinized and plugging of the orifice results. The lipid-bearing cells are replaced by keratinizing cells, and the entire process eventually results in a sac filled with keratin lamellae and retained sebaceous lipid. This is designated by the pathologists as a keratin cyst. This sequence of events which occur in the evolution of the comedo or milia of chemically induced acne and are similar to the cutaneous events which occur in acne vulgaris. The chemical stimulus invokes a perifollicular inflammatory response which may become severe and result in a breakdown of tissue and abscess formation. The process is frequently complicated by secondary infection. A test system which is offered to assess the potential of a chemical agent for inducing acne uses the rabbit ear. It was developed by Adams et al. (*30*).

Unhygienic exposures to cutting oils frequently cause folliculitis. This may be the result of follicular or perifollicular irritation. It may be complicated by acne and frequently accompanied by bacterial infection.

Of some interest are the chemicals employed in industry that have a specific toxic effect on follicular epithelium and cause hair loss. The most potent alopeciogenic substances are thallium and the dimers of chloroprene found in neoprene manufacturing. The chloroprene dimers, which are structurally related to vitamin A, appear to interfere with the metabolism of the hair-forming or matrix cells and prevent normal keratinization. This hair loss is completely reversible. Hair shaft breakage can be caused by exposure to alkaline substances or substances which break disulfide linkages in keratin, such as thioglycollates.

Pigmentary Disturbances

Occupational environments may alter pigment formation in several ways (*12*). The inciting factor may lead to either local hyperpigmentation or to a reduction of pigmentation. In most instances the pathologic process can be explained on the basis of interference with the biochemical synthesis of melanin and disturbances of one or more of the physiologic factors regulating melanin formation (*31–35*). For example, ultraviolet rays may increase pigmentation in at least five different ways. (1) Ultraviolet energy catalyzes the oxidation of tyrosine to dopa. (2) The concentration of sulfhydryl containing compounds in human epidermis may be decreased after irradiation with ultraviolet light. Sulfhydryl in a GSH tripeptide is a physiologic inhibitor of melanin formation; and when it is removed, increased pigmentation may occur. (3) The redox potential of human skin decreases appreciably after irradiation. (4) Skin temperature is frequently increased with exposure to actinic radiation. Melanin formation is accelerated under such conditions. (5) Ultraviolet energy causes darkening of melanin already present in the skin.

Chemical materials which are phototoxic agents and enhance the action of ultraviolet light on the skin include such materials as coal tar products, low-boiling petroleum products, essential oils, such as bergamot, angelica root, cumin; psoralens, and photoinitiators used in inks such as amyl *p*-aminobenzoates. Other agents may increase the degree of inflammatory reaction to erythematogenic wave lengths and cause hyperpigmentation at the exposed site. Inflammatory processes in the skin may also result in residual hyperpigmentation.

Decrease in pigmentation or pigment loss (leukoderma) may be acquired in industrial exposures to agerite alba, a rubber antioxidant which is the monobenzylether of hydroquinone. One can suspect that its effect lies in the fact that the latter substance is chemically very similar to the quinone intermediates evolved in melanin synthesis, and it probably competes for the enzyme tyrosinase with such compounds as dopaquinone. The agerite alba may veritably remove the tyrosinase from the reaction and cause a halt in new melanin formation.

Eccrine Sweat Gland Reactions

A cutaneous problem of considerable importance which is provoked by working environments in which the environmental temperature is high is prickly heat, or miliaria rubra (*12*). The pathogenesis of this disease has been ascertained and lesions reproduced in experimental subjects. The orifice and upper portion of the sweat duct may, in hot humid atmospheres, become occluded by maceration of keratin and through irritation. This occurs especially in environments in which

chemical agents may cause some damage to the duct orifice. Epidermal injury produces abnormal keratinization and hyperkeratotic plugging of the duct orifices. When the glands are subsequently stimulated thermally, sweat is trapped in the plugged ducts. As pressure increases the sweat breaks through the duct wall and extravasates into the skin, resulting in vesicle formation. The inflammatory response and pruritus may result in severe discomfort. In World War II, among American troops in the South Pacific Theatre, prickly heat was one of the major causes of incapacitation of combat personnel.

Collagen and Elastic Tissue Damage

Collagen and elastic tissue degeneration and fragmentation are among the cutaneous effects of prolonged exposure to sunlight (*12*). Persons who work out-of-doors, such as farmers, ranchers, road construction workers and sailors, are more likely to exhibit these tissue changes. Among the chronic effects of overexposure to ionizing radiation (radiodermatitis), sclerotic, degenerating collagen fibers are generally observed.

Blood Vessel Changes

The blood vessels of the skin are notably reactive to irritants and sensitizers (*12*). They are singularly damaged in prolonged low temperature exposures as in pernio, immersion foot, and frostbite. The blood vessels constitute an area of fundamental pathologic change resulting from prolonged and excessive exposure to ionizing radiation. The vessel walls become fibrotic with varying degrees of occlusion leading to ischemic changes, including atrophy, necrosis and ulceration. Chronic ionizing radiation effects are also manifested by irreversible dilatation of the capillaries and telangiectasia.

Cancer

Skin cancer is the most common form of cancer among Caucasian populations (*36*). Historically it was the first form of cancer associated with occupational factors. Percival Potts described scrotal cancer among chimney sweeps in 1775.

The most common inciting factor of skin cancer in humans is ultraviolet radiation from excessive sunlight exposure. The types of cancer associated with solar radiation (*33, 37–42*) are keratoses, basal cell carcinomas, squamous cell carcinomas, and kerato-acanthomas. Recently it has been demonstrated epidemiologically that sunlight plays a role in malignant melanoma. There is a significant genetic factor in human skin cancer from ultraviolet radiation which is characterized by hypersusceptibility (*36, 38*). The phenotype characteristics associated with skin cancer are fair complexion, light eye color, light original hair color, poor ability to tan, and frequent sunburn. Certain hereditary diseases are characterized by high susceptibility to developing ultraviolet radiation-induced skin cancers. They are albinism, xeroderma pigmentosum, and erythropoetic protoporphyria.

Polycyclic aromatic hydrocarbons, compounds found as products of combustion, degradation and fractionation of fossil fuels and other carbonaceous materials, inorganic arsenic compounds and ionizing radiation, are known to induce cancer of the skin as well as of other organ systems in man (*36, 39*). There is clinical evidence that cutaneous trauma, excessive heat, burns, bone infection such as osteomyelitis, and chronic chemical injury may be associated with the production of skin cancer (*36, 39*).

Cancer of the skin from environmental agents is preventable, easily diagnosed and, except for melanomas, curable.

Because of the accessibility and ease with which neoplasms may be induced, the skin has been utilized for many years as a model system for studying carcinogens *in vivo* and continues to be used as an essential test system in experimental animals for identifying carcinogens and quantitating neoplastic activity.

Sensory Perception Problems

While cutaneous sensation is informative as well as protective, potential and actual damage will be signaled by several sensory modalities. Pain, for example, is experienced with injury by specific mechanical trauma, radiation, heat, cold, electrical energy, and chemical irritants. It is experienced with a severe inflammatory response to infection. Itching is apparently a variant of pain, subserved by the same receptors and nerve fibers and elicited by stimuli which are quantitatively lower than the threshold level for pain. It is an ever-present symptom of many skin diseases, including those of occupational origin. The superficial inflammatory reactions provoked by primary irritants and allergic sensitizers are characterized by pruritus as well as the objective signs of inflammation.

Skin as a Model System for the Study of Biological Processes

The list of research models in which the skin can be used in experimental whole animal, in culture

systems, and/or in man is rather long. Study areas in which the skin or its components are used in model systems include percutaneous absorption, molecular transfer of chemical agents through membranes, barrier function, protein synthesis, keratinization, lipid metabolism, eccrine physiology and pathology, vascular permeability and function, thermal regulation, sensory perception, collagen synthesis and metabolism, DNA injury and repair, melanin biosynthesis, inflammation, cell-mediated and humoral hypersensitivity, phototoxicity and photoallergy, carcinogenesis, and wound healing.

The Public Health Problem Vs. Research Needs

Epidemiological information regarding cutaneous involvement in environmentally induced disease is meager. Data which are available are limited largely to occupational skin diseases. These are mostly gleaned from State Workmen's Compensation statistics which vary enormously in quality and accuracy. The variability is influenced by accuracy of records, level of industrial development and types of industry found in any one state. About 20% of occupational skin disease is of allergic origin and 80% of irritant origin or involving some other form of response. In 1973 occupational disease statistics from California indicated that skin disease accounts for 40% of all diseases and that poison oak dermatitis alone accounted for 23% of all skin conditions. Eczematous dermatitis has the highest cutaneous morbidity rate in the U. S. of all skin diseases. Primary irritant dermatitis, allergic eczematous contact dermatitis, and atopic dermatitis constitute the bulk of the eczematous dermatitis problems. Those cases of atopic origin are influenced considerably by multiple environmental factors as well. Of the irritant induced problems, the most common and the most difficult to manage clinically are those due to marginal irritants. These are chemical agents or combinations of them which produce reactions only after repeated exposure. These reactions may persist tenaciously despite removal from exposure.

While not large in number by comparison to the eczematous problems, the remainder of the cutaneous disease patterns, e.g. acne, folliculitis, hair problems, pigmentary disturbances, benign and malignant neoplasms, constitute a major challenge. New chemicals, industrial processes and consumer products may have the potential for producing such adverse health effects.

A careful scrutiny of the critical areas of environmentally induced or related skin problems and the model systems in which the skin can be used as a model for study, reveal a large number of research needs.

Surveillance Program

As in the case of most environmental and especially occupational hazards, there is an urgent need to develop significant information through surveillance and epidemiologic programs which would identify cutaneous hazards, especially in the workplace, and quantitate the scope and extent of the hazards and their biologic effects.

RECOMMENDATION 1: A workable national surveillance and fact-finding system should be developed to identify and quantitate cutaneous health problems and their specific environmental sources. This should be done especially for hazards of the workplace. National and regional mechanisms should be provided for determining the type and frequency of skin disease, duration and extent of disability, as well as economic impact. Such mechanisms would require cooperation of other health agencies which have responsibility for developing epidemiological information such as NIOSH, OSHA, FDA, and EPA.

Percutaneous Absorption

The most important cutaneous defense is the epidermal barrier, and the critical physiological factor which influences the pathogenesis of environmental skin disease is the percutaneous absorption process. A number of factors are recognized as enhancing penetration and its biological consequences, cutaneous injury and/or systemic effects. These include humidity, hydration of the stratum corneum, solubility factors, physical damage and chemical alteration of the barrier. The total research effort in the U.S.A. devoted to the elucidation of penetration mechanisms and barrier functions is currently very small. It should be expanded in scope and depth.

RECOMMENDATION 2: Systematic research in as well as the development of new models for studying percutaneous absorption should be encouraged. These efforts should be devoted to the biochemical determinants of barrier function; the further elucidation of the biochemical and physiological aspects of penetration as they may be affected by hydration; by the action of specific organic solvents; and by the molecular structure of the penetrant, its polarity and solubility characteristics. The development of new methods for deterring skin penetration should be undertaken.

Nonallergic Inflammatory Reactions

A major skin problem arising in the workplace from household and other uses is the eczematous dermatitis arising from irritants; most of such incidents stem from exposure to what are presumed to be marginal irritants. These are chemical agents or combinations of them which only produce irritant injury after repeated exposure. They include common surfactants, edible oils, a large number of organic solvents, cosmetic and toilet goods components. The amount of research devoted to sorting out the facts in nonallergic inflammatory skin reactions has been meager. Understanding the nature of primary irritant dermatitis and the manner in which injury is produced can provide an effective bridge to the control of this common skin disease.

RECOMMENDATION 3: Studies should be undertaken to elucidate the structural (cellular) and biochemical aspects or characteristics of nonallergic inflammation reactions (primary irritation) and to determine differences in pathophysiologic patterns as influenced by molecular characteristics of the irritant, the rates of penetration, metabolism of the irritant, lysosomal and kinin activity, etc. Efforts should be focused on the ubiquitous marginal irritant. There is a need to correlate molecular structure and electrochemical forces with irritant capacity. There is a need to examine action of marginal irritants on cell organelles. Among aliphatic acids in the range of C_2 to C_{20}, peak irritation occurs at C_{12}. There is a steady rise in skin irritant capacity from C_2 to C_{12} then falling off so that C_{18} acid has a very low capacity. It is also of some interest to note that C_{12} chain length in alkanes, such as dodecane, and in dodecylbenzene is a potent accelerator of carcinogenesis. A study of the biological significance of the C_{12} chain length would appear to be important.

Accommodation

Another intriguing observation in the skin irritation story is the accommodation phenomenon. Following repeated exposure to an irritant, both human and animal skin are capable, with continuous exposure, of demonstrating either complete healing, nonresponsiveness, or decrement of response. In guinea pigs and man this has been observed with fatty acids, aliphatic alcohols, and synthetic detergents.

RECOMMENDATION 4: Studies should be developed to determine the cellular and biochemical or metabolic factors which are associated with "turning off" the inflammation response with continued exposure. The phenomenon should be examined at the cellular and subcellular level, using electron microscopy. The protein, carbohydrate, and lipid components of the normal, irritated and "turned off" skin should be examined, as well as the role of lysosomal components, kinins, etc.

Allergic Cutaneous Response

The public health problem involving environmental agents which are potential antigens and which may result in disabling eczematous allergic dermatitis, is a large one. There are a wide variety of chemicals currently used in industrial processes and in consumer products, and new agents which are being introduced continuously which need appraisal for immunobiologic activity. Some of them are intriguing because judging from their structure one would not anticipate antigenicity, e.g., ethyl alcohol. Others are simple chemical compounds, inorganic or organic, which may be sensitizing in one molecular form but not in a closely related one. Little effort has been exerted in attempting to relate sensitizing capacity and the mechanisms involved to molecular structure; or in studying at the cellular or biochemical level allergic sensitization by small molecules. There is some controversy about the types of tests now being employed to identify and quantify the effects of contact allergens. There is a need to determine relative merit of each test system, and to equate such results with human use experience. There is also a need for development work in this area for more effective and sensitive test models.

RECOMMENDATION 5: Modern skills of immunobiology and immunochemistry should be applied for the elucidation of mechanisms of allergic cutaneous responses, particularly the contact type. Substances such as the transitional metals, nickel, chromium, plastic monomers, aldehydes, alcohols, phenols, ketones, and coumarins should be studied in depth. Critical aspects requiring examination are the role of molecular structure, metabolism by mammals, protein combining characteristics, effect on macrophages, lymphocytes, etc., as well as interferences or enhancement of sensitizers by other environmental agents. Studies should address themselves to the quenching or blocking phenomenon observed with aroma aldehydes.

PCBs

The environmental agents which affect sebaceous structures most severely and cause generalized acne have serious systemic effects as well. The family of compounds about which there is great concern was found until recently in many industrial and

consumer uses and includes chlorinated diphenyls, diphenyl oxides, and chlorinated dibenzodioxins. Some of these agents have produced severe health effects of epidemic proportions. Among such effects are industrial chloracne and Yusho, which include acne and hyperpigmentation. Other known health effects which may be severe are hepatic and neurologic damage and teratologic effects, the last of which have been observed in experiments with animals. The long-term effects and relationships between effects on different organ systems have not been systematically studied.

RECOMMENDATION 6: Epidemiologic studies should be undertaken to determine the long-term cutaneous effect of polychlorinated biphenyls (PCBs) in humans. Populations evaluated should include those exposed in the workplace as well as those exposed through ecologic transfer, e.g., through water or food. Acnegenic agents, such as PCBs, require in-depth studies to determine biologic mechanisms involved in the pathogenesis of adverse skin effects. Attention should be given to the action of PCBs and metabolites on sebaceous cells, on keratinocytes, on lipid metabolism, on cutaneous flora which produce lipolytic enzymes, on endocrine activity including direct or indirect androgenic effects, and on pigmentation and its relation to porphyrin metabolism and ultraviolet radiation reactivity. Every attempt should be made to correlate or coordinate these efforts with studies on neurotoxicity, gonadotoxicity, hepatotoxicity or on the mutagenic, teratogenic, and carcinogenic potential of these same compounds.

Carcinogens

Skin cancer has its highest incidence among Caucasian populations. The most important single cause is exposure to ultraviolet radiation from solar sources. The types of skin neoplasm induced are keratoses, basal cell carcinomas, squamous cell carcinomas, and keratoacanthomas. There is now evidence that sunlight also plays a significant role in the pathogenesis of malignant melanoma. Hypersusceptibility to ultraviolet radiation cancer is genetically determined. Certain hereditary diseases such as xeroderma pigmentosum and albinism are characterized by high susceptibility to developing ultraviolet radiation-induced cancer. One of the genetic defects in xeroderma is the inability to repair ultraviolet-induced DNA injury in cutaneous cells. DNA damage which is not lethal allows for persistence of transformed cells. In addition to ultraviolet radiation, ionizing radiation, burns, skin trauma, and chronic infection are associated with the development of squamous cell carcinoma. Among the chemical agents found in the environment, combustion, fractionation and degradation products of fossil fuels containing specific polycyclic aromatic hydrocarbons and mixtures of them, as well as inorganic compounds of arsenic, are associated with skin cancer in man. These and/or closely related substances will induce cancer of the lung as well. Skin tumors in experimental animals can be reproduced in animals by repeated exposure to the suspected agent except in the case of arsenic. Finally, the skin provides an accessible test system for identifying carcinogens and quantitating neoplastic activities. One of the most intriguing problems in skin carcinogenesis is the combined action of ultraviolet radiation and chemical agents which absorb ultraviolet radiation. It has been shown that long-wave ultraviolet radiation (365 nm), which alone will not induce skin cancer at even high energy levels, will induce tumors in 100% of mice if the animal is treated with a phototoxic agent such as methoxypsoralen which alone is not carcinogenic. Such combinations will cause interstrand crosslinking between psoralens and DNA, and mutations in mammalian cells. Enhancement of carcinogenic properties of certain ubiquitous polycyclic aromatic compounds from fossil fuel uses will also occur when exposure to ultraviolet radiation occurs at the same time. With the current need to develop energy sources, new processes are being developed and used for producing fuel by the liquefaction or gasification of coal and by the refining of oil shale. Historically, refining processes of these fuel sources evolved products which were potent carcinogens for human and mouse skin.

RECOMMENDATION 7: To understand the nature of carcinogenesis in general and the pathogenesis of skin tumors in particular, studies should be devoted to the examination of mutagenesis in skin cell models both *in vitro* and *in vivo*. Suspect groups such as chlorinated hydrocarbons, vinyl chloride, styrene and its epoxides, arsenic, nickel, and chromium compounds should be explored. The biochemical aspects and immunologic aspects of cell transformation and tumorigenesis by these additional suspect compounds should be systematically studied. Test models using cell cultures, as well as skin in whole animals including man, can be used to detect mutagenic phenomena including the effects of environmental agents on DNA repair after injury.

It is necessary to identify the large number of photoactive agents being used in a wide variety of industrial processes and in consumer products, including cosmetics and drugs, so that users can be protected against exposure. While the hazard of phototoxicity itself is not too serious, the possibility

of the combined exposure being mutagenic and/or carcinogenic is the major risk which needs to be identified and controlled.

The mutagenic and carcinogenic properties of components of new fossil fuel process streams should be systematically and carefully assessed before the processes are used for full-scale production.

Test Methods

While some attention has been given by cutaneous biologists, dermatologists, and toxicologists to the development and/or improvement of test methods for predicting cutaneous hazards, there is an urgent need for careful appraisal of current methods and a greater need for the development of new methods especially for assessing adverse effects other than contact sensitization or photosensitization. For example, there is a critical need to develop better methods of detecting ubiquitous marginal irritants, acnegenic substances, chemicals which produce granulomas, and substances or processes which alter pigment. Animal and human skin as well as cells in culture are readily accessible models which can be utilized for development work.

RECOMMENDATION 8: More sensitive methods should be developed for predicting adverse response to primary irritants (especially those of a marginal nature), to acnegenic substances, and to chemical and physical agents or combinations of those which induce pigment changes. With the array of tests available for predicting allergenicity, a serious attempt should be made to compare the sensitivity and reliability of these tests in relation to clinical experience.

This material is drawn from a Background Document prepared by the author for the NIEHS Second Task Force for Research Planning in Environmental Health Science. The Report of the Task Force is an independent and collective report which has been published by the Government Printing Office under the title, "Human Health and the Environment—Some Research Needs." Copies of the original material for this Background Document, as well as others prepared for the report can be secured from the National Technical Information Service, U. S. Department of Commerce, 5285 Port Royal Road, Springfield, Virginia 22161.

REFERENCES

1. Johnson, M. L. Disability, American Academy of Dermatology, 1969, pp. 46 and 48.
2. Rothman, S., and Lorincz, A. L. Defense mechanisms of the skin. Ann. Rev. Med. 14: 215 (1963).
3. Lobitz, W. C., Jr., and Daniels, F., Jr. Skin. Ann. Rev. Physiol. 23: 207 (1961).
4. Nicoll, P. A., and Cortese, T. A., Jr. The physiology of skin. Ann. Rev. Physiol. 34: 177 (1972).
5. Weinstein, G. D., et al. Biochemistry and physiology of the epidermis and its appendages. In: Dermatology in General Medicine. T. B. Fitzpatrick, et al., Ed. McGraw-Hill, New York, 1971, pp. 78-116.
6. Scheuplein, R. J. Properties of the skin as a membrane. Adv. Biol. Skin. 12: 125 (1972).
7. Scheuplein, R. J., and Blank, I. H. Permeability of the skin. Physiol. Revs. 51: 702 (1971).
8. Blank, I. H. Transport across the stratum corneum. Toxicol. Appl. Pharmacol. (Suppl. No. 3) 23 (1969).
9. Suskind, R. R. Percutaneous absorption of chemicals. Paper presented at Symposium on Environmental and Physiologic Chemodynamics, Oregon State University Environmental Health Sciences Center, Corvallis, Oregon, January 9, 1969.
10. Tregear, R. Molecular movement the permeability of skin. In: Physical Functions of Skin. Academic Press, New York, 1966, pp. 1-52.
11. Malkinson, F. D., and Rothman, S. Percutaneous absorption. In: Handbuch der Haut- und Geschlechtskrankheiten. J. Jadassohn, Ed., Springer-Verlag, Berlin, Vol. 1, part 3, 1963, pp. 90–156.
12. Suskind, R. R. Occupational skin problems. I. Mechanisms of dermatologic response. J. of Occup. Med. 1: 39 (1959).
13. Suskind, R. R., and Majeti, V. A. Occupational and environmental allergic problems of the skin. J. Dermatol. 3: 3 (1976).
14. Klecak, G., et al. Screening of fragrance materials for skin irritation and allergenicity in guinea-pigs. I. Single chemical compounds. in preparation.
15. Klecak, G., Geleick, H., and Frey, J. R. Screening of fragrance materials for allergenicity in the guinea-pig. I. Comparison of four testing methods. J. Soc. Cosmet. Chem. 28: 53 (1977).
16. Malten, K. E. Occupational dermatoses in the processing of plastics. Trans. St. John's Hosp. Dermatol. Soc. 59: 78 (1973).
17. Fisher, A. A. Contact Dermatitis. Lea and Febiger, Philadelphia, 1973.
18. Spector, W. G., and Willoughby, D. A. Vascular and cellular aspects of inflammation of the skin. Adv. Biol. Skin. 11: 29 (1971).
19. David, J. R. Lymphocytic factors in cellular hypersensitivity. In: Immunobiology. R. A. Good and D. W. Fisher, Eds., Sinauer Associates, Stamford, Conn., 1971, pp. 146-56.
20. Magnusson, B., and Kligman, A. M. Allergic contact dermatitis in the guinea pig: Identification of contact allergens. Charles C Thomas, Springfield, Ill., 1970.
21. Waksman, B. H. Delayed hypersensitivity; Immunologic and clinical aspects. Hosp. Practice 3: 22 (Aug. 1968).
22. Kligman, A. M. The identification of contact allergens by human assay. III. The maximization test: A procedure for screening and rating contact sensitizers. J. Invest. Dermatol. 47: 393 (1966).
23. Spector, W. G., and Willoughby, D. A. Vascular and cellular aspects of inflammation of the skin. Adv. Biol. Skin. 11: 29 (1971).
24. Draize, J. H. Dermal toxicity. In: Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics. Association of Food and Drug Officials of the United States, Topeka, Kansas, 1959, pp. 46–59.
25. Kimbrough, R. D. The toxicity of polychlorinated polycyclic compounds and related chemicals. Crit. Revs. Toxicol. 2: 445 (1974).
26. Suskind, R. R. Chloracne and associated problems. Paper

presented at the NIEHS Conference on Dibenzodioxins and Dibenzofurans, Research Triangle Park, N. C., April 3, 1973.
27. Kuratsune, M., et al. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. Environ. Health Perspect. 1: 119 (1972).
28. Suskind, R. R. Cutaneous response to industrial acnegens. Paper presented at American Academy of Dermatology, Symposium on the Physiology and Chemistry of the Skin. Chicago, Ill., Dec. 10, 1957.
29. Crow, K. D. Chloracne. A critical review including a comparison of two series of cases of acne from chlornaphthalene and pitch fumes. Trans. St. John's Hosp. Dermatol. Soc. 56: 79 (1970).
30. Adams, E. M., et al. The response of rabbit skin to compounds reported to have caused acneform dermatitis. Ind. Med. Ind. Hyg. 2: 1 (1941).
31. Fitzpatrick, T. B., et al., Eds. Dermatology in General Medicine. McGraw-Hill, New York, 1971, Chapt. 5.
32. Smith, K. C. The cellular repair of radiation damage. In: Sunlight and Man; Normal and Abnormal Photobiologic Responses. M. A. Pathak et al., Eds., University of Tokyo Press, Tokyo, 1974, pp. 67–77.
33. Fitzpatrick, T. B., et al. An introduction to the problem of normal and abnormal responses of man's skin to solar radiation. In: Sunlight and Man: Normal and Abnormal Photobiologic Responses. M. A. Pathak et al., Eds., Univ. Tokyo Press, Tokyo, 1974, pp. 3–14.
34. Smith, K. C. Molecular changes in the nucleic acids produced by ultraviolet and visible radiation. In: Sunlight and Man: Normal and Abnormal Photobiologic Responses. M. A. Pathak, et al., Eds., University of Tokyo Press, Tokyo, 1974, pp. 57–66.
35. Epstein, J. H. Photoallergy. Arch. Dermatol. 106: 741 (1972).
36. Emmett, E. A. Occupational skin cancer: a review. J. of Occup. Med. 17: 44 (1975).
37. Suskind, R. R. Ultraviolet radiation carcinogenesis: UVR and atmospheric contaminants. In: Sunlight and Man: Normal and Abnormal Photobiologic Responses. M. A. Pathak, et al., Eds., Univ. of Tokyo Press, Tokyo, 1974, pp. 285–98.
38. Emmett, E. A. Ultraviolet radiation as a cause of skin tumors. Crit. Revs. Toxicol. 2: 211 (1973).
39. Suskind, R. R., and Horton, A. W. Etiologic factors and the pathogenesis of premalignant and malignant lesions. In: The Human Integument, Normal and Abnormal. S. Rothman, Ed., American Association for the Advancement of Science, Washington, D. C., 1959, pp. 171–92.
40. Emmett, E. A. Occupational skin cancer: a review. J. Occup. Med. 17: 44 (1975).
41. Epstein, J. H. Xeroderma pigmentosum and UVL carcinogenesis. In: Sunlight and Man: Normal and Abnormal Photobiologic Responses. M. A. Pathak et al., eds., University of Tokyo Press, Tokyo, 1974, pp. 299–315.
42. Epstein, J. H. Ultraviolet carcinogenesis. In: Photophysiology. A. C. Giese, Ed., Academic Press, New York, 1970, Vol. 5, pp. 235–73.